Attorney's Docket No.: 07039-119001

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Svetomir N. Markovic
Serial No. : 09/187,385
Filed : November 6, 1998
Title : INTERFERON IMMUNOTHERAPY

Art Unit : 1642
Examiner : Holleran, A.

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION UNDER 37 C.F.R. § 1.132

I, Svetomir N. Markovic, declare as follows:

1. I am employed at Mayo Clinic, 200 First Street Southwest, Rochester, Minnesota, 55905.

2. I am the sole inventor of the subject matter described and claimed in the above-referenced patent application.

3. I have read the Office Action mailed July 1, 2003, for the above-referenced patent application. I also have read the Tovey *et al.* patent cited in this Office Action.

4. I, or individuals under my supervision, determined the immunostimulatory dosage of alpha-interferon in human patients as follows. Patients were treated with a daily dosage of alpha-interferon for five days (days 1-5). NK cytotoxicity was measured as described in Example 1 of the above patent application using an effector to target cell ratio (E:T) of 25:1, and normalized to a baseline of 1.0. A dosage was considered immunostimulatory if NK cytotoxicity was increased by at least 75% on at least one day.

CERTIFICATE OF MAILING BY FIRST CLASS MAIL

I hereby certify under 37 CFR §1.8(a) that this correspondence is being deposited with the United States Postal Service as first class mail with sufficient postage on the date indicated below and is addressed to the Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

9/30/03
Date of Deposit

Theresa Popelka
Signature

Theresa Popelka
Typed or Printed Name of Person Signing Certificate

Each patient in the first group of patients (n=5, patients 1-5) was administered a daily dosage of 250,000 U alpha-interferon/m^2 for five days. Within the first group of patients (see attached Figure 1), three of the patients had 60 to 70% increases in cytotoxicity (patients 1, 2, and 4). The dosage was immunostimulatory only for one of the five patients (patient 5).

The dosage of alpha-interferon was increased to 500,000 U/m^2 per day for five days in a second set of patients (n=5, patients 6-10) and NK cytotoxicity was measured as described above. Within the second group, overall response was lower than that of patients in the first group (see attached Figure 2). This dosage resulted in a 40-50% increase in NK cytotoxicity in two patients (patients 6 and 9), and the dosage was considered immunostimulatory in only one patient (patient 10).

The third group of patients (patients 11-15) received 325,000 U of alpha-interferon/m^2 per day for five days. Response in this set of patients was better than that of the first and second groups of patients (see attached Figure 3), as the dosage was immunostimulatory in four of the five patients (patients 11, 13, 14, and 15).

5. I believe, based on the above data, that a dosage of alpha-interferon that is less than about 250,000 U/m^2 would not be immunostimulatory in patients.

6. I believe, based on the above data, that a dosage of alpha-interferon that is greater than about 500,000 U/m^2 would not be immunostimulatory in patients.

7. I believe, based on the above data, that a dosage range of alpha-interferon from about 250,000 U/m^2 to about 500,000 U/m^2 is critical to the clinical success of the claimed methods. The criticality of this range could not have been predicted from the disclosure of the Tovey *et al.* patent.

8. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the

United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Respectfully submitted,

Date: 9/25/03

Svetomir N. Markovic

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